

What Is Claimed Is:

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1. An article of manufacture comprising packaging material and a pharmaceutical composition contained within said packaging material, wherein said pharmaceutical composition is capable of modulating angiogenesis in a tissue associated with a disease condition, wherein said packaging material comprises a label which indicates that said pharmaceutical composition can be used for treating disease conditions by modulating angiogenesis, and wherein said pharmaceutical composition comprises a Raf protein or an oligonucleotide having a nucleotide sequence capable of expressing said protein.

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2. The article of manufacture of claim 1 wherein said Raf protein is an active Raf protein and said modulating potentiates angiogenesis.

3. The article of manufacture of claim 2 wherein said active Raf protein is wild-type Raf.

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4. The article of manufacture of claim 3 wherein said active Raf protein is a fusion protein.

5. The article of manufacture of claim 4 wherein said active Raf fusion protein is Raf-caax.

6. The article of manufacture of claim 2 wherein said tissue has poor circulation.

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7. The article of manufacture of claim 1 wherein said Raf protein is an inactive Raf protein and said modulating inhibits angiogenesis.

8. The article of manufacture of claim 7 wherein said inactive Raf protein has a mutation at residue 375 such that the amino acid at position 375 is not lysine.

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9. The article of manufacture of claim 7 wherein said tissue is inflamed and said condition is arthritis or rheumatoid arthritis.

10. The article of manufacture of claim 7 wherein said tissue is a solid tumor or solid tumor metastasis.

11. The article of manufacture of claim 10 wherein said administering is conducted in conjunction with chemotherapy.

12. The article of manufacture of claim 7 wherein said tissue is retinal tissue and said condition is retinopathy, diabetic retinopathy or macular degeneration.

13. The article of manufacture of claim 7 wherein said tissue is at the site of coronary angioplasty and said condition is restenosis.

5 14. The article of manufacture of claim 1 wherein said administering comprises intravenous, transdermal, intrasynovial, intramuscular, or oral administration.

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15. The article of manufacture of claim 1 wherein said administering comprises a single dose intravenously.

10 16. The article of manufacture of claim 1 wherein said pharmaceutical composition further comprises a liposome.

17. The article of manufacture of claim 1 wherein said pharmaceutical composition comprises a viral expression vector capable of expressing said nucleotide sequence.

15 18. The article of manufacture of claim 1 wherein said pharmaceutical composition comprises an non-viral expression vector capable of expressing said nucleotide sequence.

19. A method for modulating angiogenesis in a tissue associated with a disease condition comprising administering to said tissue an angiogenesis modulating amount of a pharmaceutical composition comprising a Raf protein or a nucleotide sequence capable of expressing said protein.

20 21. The method of claim 19 wherein said Raf protein is an active Raf protein and said modulating potentiates angiogenesis.

22. The method of claim 21 wherein said active Raf protein is a fusion protein.

23. The method of claim 22 wherein said active Raf fusion protein is Raf-caax.

25 Raf.

24. The method of claim 20 wherein said tissue has abnormal circulation.

25. The method of claim 19 wherein said Raf protein is an inactive Raf protein and said modulating inhibits angiogenesis.

26. The method of claim 25 wherein said inactive Raf protein has a mutation at residue 375 such that the amino acid at position 375 is not lysine.

27. The method of claim 25 wherein said tissue is inflamed and said condition is arthritis or rheumatoid arthritis.

28. The method of claim 25 wherein said tissue is a solid tumor or solid tumor metastasis.

29. The method of claim 28 wherein said administering is conducted in conjunction with chemotherapy.

30. The method of claim 25 wherein said tissue is retinal tissue and said condition is retinopathy, diabetic retinopathy or macular degeneration.

31. The method of claim 25 wherein said tissue is at the site of coronary angioplasty and said tissue is at risk for restenosis.

32. The method of claim 19 wherein said administering comprises intravenous, transdermal, intrasynovial, intramuscular, or oral administration.

33. The method of claim 19 wherein said administering comprises a single dose intravenously.

34. The method of claim 19 wherein said pharmaceutical composition further comprises a liposome.

35. The method of claim 19 wherein said pharmaceutical composition comprises an retroviral expression vector capable of expressing said nucleotide sequence.

36. The method of claim 19 wherein said pharmaceutical composition comprises an non-viral expression vector capable of expressing said nucleotide sequence.

37. A pharmaceutical composition for stimulating angiogenesis in a target mammalian tissue comprising a viral gene transfer vector containing a nucleic acid,

50 said nucleic acid having a nucleic acid segment encoding for a Raf protein, said Raf protein having kinase activity, and a pharmaceutically acceptable carrier or excipient.

5 38. A pharmaceutical composition for stimulating angiogenesis in a target mammalian tissue comprising a non-viral gene transfer vector containing a nucleic acid, said nucleic acid having a nucleic acid segment encoding for a Raf protein, said Raf protein having kinase activity, and a pharmaceutically acceptable carrier or excipient.

10 39. A pharmaceutical composition for inhibiting angiogenesis in a target mammalian tissue comprising a viral gene transfer vector containing a nucleic acid, said nucleic acid having a nucleic acid segment encoding for a Raf protein, said Raf protein having no kinase activity, and a pharmaceutically acceptable carrier or excipient.

15 40. A pharmaceutical composition for inhibiting angiogenesis in a target mammalian tissue comprising a non-viral gene transfer vector containing a nucleic acid, said nucleic acid having a nucleic acid segment encoding for a Raf protein, said Raf protein having no kinase activity, and a pharmaceutically acceptable carrier or excipient.

20 *✓* 41. A pharmaceutical composition for stimulating angiogenesis in a target mammalian tissue comprising a therapeutic amount of a Raf protein, said Raf protein having kinase activity, and a pharmaceutically acceptable carrier or excipient.

42. A pharmaceutical composition for inhibiting angiogenesis in a target mammalian tissue comprising a therapeutic amount of a Raf protein, said Raf protein having no kinase activity, and a pharmaceutically acceptable carrier or excipient.

25 43. An article of manufacture comprising packaging material and a pharmaceutical composition contained within said packaging material, wherein said pharmaceutical composition is capable of modulating angiogenesis in a tissue associated with a disease condition, wherein said packaging material comprises a label which indicates that said pharmaceutical composition can be used for treating disease conditions by modulating angiogenesis, and wherein said pharmaceutical composition

comprises a Ras protein or an oligonucleotide having a nucleotide sequence capable of expressing said protein.

44. An article of manufacture according to claim 43 wherein said Ras protein or oligonucleotide encoding said protein is an inhibitory Ras protein.

5 45. An article of manufacture of claim 44, wherein said inhibitory Ras is Ras V12C40.

46. An article of manufacture of claim 44, wherein said inhibitory Ras is Ras S17N.

10 47. An article of manufacture according to claim 43 wherein said Ras protein or oligonucleotide encoding said protein is a stimulatory Ras protein.

48. An article of manufacture of claim 47, wherein said stimulatory Ras is Ras G12V.

49. An article of manufacture of claim 47, wherein said stimulatory Ras is Ras V12S35.

15 50. A method for modulating angiogenesis in a tissue associated with a disease condition comprising administering to said tissue an angiogenesis modulating amount of a pharmaceutical composition comprising a Ras protein or a nucleotide sequence encoding for said protein.

51. The method according to claim 50 wherein said Ras protein or oligonucleotide encoding for said protein is an inactive Ras protein.

52. The method of claim 51, wherein said inactive Ras is Ras V12C40.

53. The method of claim 51, wherein said inactive Ras is Ras S17N.

54. The method according to claim 50 wherein said Ras protein or oligonucleotide encoding for said protein is an active Ras protein.

25 55. The method of claim 54, wherein said active Ras is Ras GV12.

56. The method of claim 54, wherein said active Ras is Ras V12S35.

57. A pharmaceutical composition for modulating angiogenesis in a target mammalian tissue comprising a viral gene transfer vector containing a nucleic acid, said nucleic acid having a nucleic acid segment encoding for a Ras protein, said Ras

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protein having angiogenesis modulating activity, in a pharmaceutically acceptable carrier or excipient.

5 58. A pharmaceutical composition of claim 57, for inhibiting angiogenesis in a target mammalian tissue wherein said Ras protein has angiogenesis inhibitor activity.

59. A pharmaceutical composition of claim 58, wherein said Ras protein is Ras V12C40.

60. A pharmaceutical composition of claim 58, wherein said Ras protein is Ras S17N.

10 61. A pharmaceutical composition of claim 57, wherein said Ras protein has angiogenesis activating activity.

62. A pharmaceutical composition of claim 61, wherein said Ras protein is Ras G12V.

15 63. A pharmaceutical composition of claim 61, wherein said Ras protein is Ras V12S35.

20 64. A pharmaceutical composition for modulating angiogenesis in a target mammalian tissue comprising a non-viral gene transfer vector containing a nucleic acid, said nucleic acid having a nucleic acid segment encoding for a Ras protein, and said Ras protein having angiogenesis modulating activity, and a pharmaceutically acceptable carrier or excipient.

25 65. A method for modulating angiogenesis in a tissue associated with a disease condition comprising administering to said tissue an angiogenesis modulating amount of a pharmaceutical composition comprising a Raf protein or a nucleotide sequence capable of expressing said protein, and a Ras protein or a nucleotide sequence capable of expressing said protein.

66. A method of claim 65 wherein said modulation is an inhibition of angiogenesis, and at least one of said Raf and Ras proteins are inactive.

67. A method of claim 65 wherein said modulation is an stimulation of angiogenesis, and at least one of said Raf and Ras proteins are active.